Agreement between Self- and Clinician-Collected Specimen Results for Detection and Typing of High-Risk Human Papillomavirus in Specimens from Women in Gugulethu, South Africa[▽]

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We assessed the agreement in detection of high-risk human papillomavirus (HPV), as well as specific HPV types, between self- and clinician-obtained specimens for 450 women over 18 years of age attending a community health center in Gugulethu, South Africa. Both self-collected swabs and tampons had high agreement with clinician-obtained brushes when the Roche Reverse Line Blot Assay (RLBA) was used (for swabs, 86% concordance, with a kappa statistic [κ] of 0.71; for tampons, 89% concordance, with κ of 0.75). Agreement was lower, although still fair, with the Digene Hybrid Capture 2 test (HC2), with κ higher for swabs than for tampons (for swabs, 81% concordance, with κ of 0.61; for tampons, 82% concordance, with κ of 0.55). Low-risk HPV types were nearly two times more common in self-collected specimens than in clinician-collected specimens tested by RLBA. All 15 women diagnosed with high-grade lesions by cytology tested positive for high-risk HPV with clinician-collected specimens tested by RLBA and HC2, while 11 out of 15 tested positive with self-collected specimens by HC2 and 5 out of 6 tested positive by RLBA. Self-collected specimens can provide valid specimens for HPV testing using nucleic acid amplification tests, although a few cytological abnormalities may be missed.

An estimated 493,000 new cases of cervical cancer occur each year, with over 80% occurring in developing countries (7, 17). While Papanicolaou (Pap) screening programs have led to significant declines in cervical cancer mortality rates in developed countries, they have been less successful in resource-poor settings, as they require significant clinical and laboratory infrastructure, trained cytologists or pathologists, and frequent patient visits due to the relatively low sensitivity (1, 2). Human papillomavirus (HPV) testing is being promoted increasingly as a screening test for women over 30 years old, as it is more sensitive than the Pap smear and identifies a subgroup of women positive for high-risk HPV who require further cytology (11).

The “gold standard” for obtaining specimens to detect HPV is for a clinician to use an endocervical brush during a speculum examination. However, this procedure is invasive and time

consuming; requires private clinic space, a gynecological table, and sterilizing equipment; and, in some instances, is not culturally acceptable (16). Therefore, alternative sampling methods, such as self-obtained swabs or tampons, are needed. Self-sampling for HPV diagnosis has been tried in a number of settings (3, 5, 6, 8–10, 12–15, 18, 20–22, 25). However, few studies have been implemented in Africa (14, 22, 25), and few have compared HPV type-specific identification between clinician- and self-obtained specimens (3, 8, 20, 21).

The goal of this study was to determine the agreement between clinician-obtained endocervical brush specimens during a speculum examination and self-sampling with swabs or tampons for high-risk HPV in general, as well as for individual types, in women attending a community health center in Gugulethu, South Africa. Cytology results were also compared with HPV results.

MATERIALS AND METHODS

The aim of the study was to enroll 450 women recruited from the NY1 Community Health Center in Gugulethu, South Africa, a resource-poor, peri-urban area adjacent to Cape Town: 150 women attending the clinic with reproductive tract infection (RTI) symptoms (RTI group) and 300 attending for any other reason (non-RTI group). Half of the women in each group were asked to self-sample using a tampon and half using two vaginal swabs, by systematic

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allocation. A nurse performed a speculum exam on every woman to obtain a Pap smear and vaginal and endocervical specimens. Half of the women self-sampled first, and half had a speculum exam first, with 15 to 20 min between procedures. A counselor administered a structured questionnaire on demographics and sexual behavior, followed by counseling on RTIs and safer sex.

Women were eligible to participate if they were 18 years or older, sexually active, self-reportedly not pregnant, and willing to comply with the protocol and gave written informed consent. They were excluded if they had taken antibiotics in the previous 4 weeks, were participating in a study evaluating a vaginal product, or had a history of sensitivity to latex. The protocol was approved by ethics committees of the University of Cape Town and the Population Council.

The self-collected tampon or swab and paired clinician-obtained specimen were tested for HPV at the University of Cape Town with the Digene Hybrid Capture 2 (HC2) High-Risk HPV test (Digene Corporation, Gaithersburg, MD). The Roche Reverse Line Blot Assay (RLBA) (Roche Molecular Systems Inc., Branchburg, NJ) was used to detect 27 HPV genotypes with the first 183 paired specimens. Specimens were also used to test for several other infections, as reported previously (24).

Women in the tampon group inserted a non-applicator mini-tampon for light menstrual flow (Lil-lets; Accantia, Solihull, United Kingdom), removed it after 10 min, placed it, holding its string, into a sterile 50-ml universal container prefilled with 12 ml of phosphate-buffered saline, and pushed it down with a clean swab. A nurse later removed the tampon, placed it into a disposable funnel inserted into a clean tube, and squeezed it against the side of the funnel using her gloved index finger to collect a minimum of 2.5 ml of tampon-derived fluid.

Women in the vaginal swab group inserted two vaginal swabs high into the vagina and swirled them around while squatting. A nurse then placed one swab into Digene transport medium.

During each speculum examination, samples were collected with a Digene cervical sampling brush placed in Digene transport medium, a cytobrush for a Pap smear, and four vaginal swabs and one endocervical swab for other pathogens (24). Vaginal swabs were collected first, followed by the cervical brush and cytobrush.

Specimens were delivered at room temperature to the laboratory at the end of each work day and immediately frozen at -20°C until being tested. Pap smears were sent to the cytology laboratory of the University of Limpopo and classified according to the Bethesda system as normal or as having atypical squamous cells of undetermined significance (ASCUS), atypical glandular cells of undetermined significance (AGUS), low-grade squamous intraepithelial lesions (LSIL), or high-grade squamous intraepithelial lesions (HSIL). Women with abnormal results were referred to Groote Schuur Colposcopy Clinic. Women were not told their HPV results, as care was based on cytology results. All women received a syphilis blood test and were offered human immunodeficiency virus testing and condoms at no cost.

Statistical analysis. Specimens were considered positive for high-risk HPV by the HC2 test at the standard cutoff value of 1.0 relative light units (RLU) or 1 pg of HPV DNA/ml (23). For the 183 paired specimens tested by RLBA, 15 HPV types were considered high-risk: HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -68, -73, and -82 (17). HPV-26, -53, and -66 were considered probable high-risk types, and HPV-6, -11, -40, -42, -54, -55, -57, -83, and -84 were considered low-risk types (17).

Analyses were conducted with SAS, version 9.0 (SAS Institute Inc, Cary, NC). Differences between sampling methods and recruitment groups were compared with the two-tailed Fisher exact test for unordered categorical variables, the Kruskal-Wallis test for ordered categorical variables, and the Mann-Whitney rank sum test for continuous variables. Two-tailed exact 95% confidence intervals (CI) for proportions were calculated with the binomial option in SAS. The kappa statistic (κ) was used to compare agreement of HPV status results between clinician- and self-collected specimens, with the two-tailed chi-squared test for equal κ coefficients used to determine significant differences between the tampon and the swab at a probability level of 0.05. The McNemar test was used to test for significant differences between paired clinician- and self-obtained HPV distributions. Calculations of sensitivity and specificity used clinician-collected specimen results to define true cases.

RESULTS

Between January and August 2002, 476 women were assessed for eligibility to participate in the study and 450 were enrolled. All 450 underwent a clinician-directed speculum examination; 222 self-sampled using swabs and 228 using a tam-

TABLE 1. Baseline HPV and Pap smear results by recruitment group

Result	No. (%) with indicated result		
	Non-RTI services (<i>n</i> = 300)	RTI services (<i>n</i> = 150)	Total (<i>n</i> = 450)
HPV positive by HC2			
Clinician collected	101 (33.8)	62 (41.3)	163 (36.3)
Self-collected	94 (31.3)	56 (37.6)	150 (33.4)
HPV positive by RLBA ^a (<i>n</i> = 183)			
Clinician collected	52 (43.0)	31 (50.0)	83 (45.4)
Self-collected	58 (47.9)	33 (53.2)	91 (49.7)
Cytology result (<i>n</i> = 441)			
Normal	245 (83.6)	123 (83.1)	368 (83.4)
ASCUS	13 (4.3)	8 (5.3)	21 (4.7)
AGUS	23 (7.7)	12 (8.0)	35 (8.0)
LSIL	2 (0.7)	2 (1.3)	4 (0.9)
HSIL	12 (4.0)	3 (2.0)	15 (3.3)

^a Positive RLBA is defined as positive for any of the 27 HPV types tested.

pon. High-risk HPV infections were common in both recruitment groups, with 36% of clinician-collected specimens positive by HC2 (Table 1). Forty-two percent of women under 30 tested positive with clinician-collected specimens, compared to 30% of women over 30 ($P = 0.075$).

We found strong agreement in HPV results for all types combined between clinician-collected and self-collected specimens in combination with RLBA testing (overall κ , 0.73; 87% concordance), with little difference between swab results and tampon results (for swabs, 86% concordance, with κ of 0.71; for tampons, 89% concordance, with κ of 0.75) (Table 2). In terms of HC2, of 163 women with HC2-positive clinician-collected specimens, 114 also had HC2-positive self-collected specimens, corresponding to a sensitivity of 70% (95% CI, 62 to 77%), a specificity of 87% (95% CI, 83 to 91%), and 81% concordance, with an overall κ of 0.58. Lowering of the cutoff value to 0.3 RLU increased this sensitivity to 86% but decreased specificity to 66%. Self-sampling with swabs resulted in significantly higher sensitivity (80% versus 60% [$P = 0.005$]) and lower specificity (83% versus 92% [$P = 0.019$]) than with tampons. Furthermore, the κ statistic was higher for swabs than for tampons, although not significantly so (for swabs, 81% concordance, with κ of 0.61; for tampons, 82% concordance, with κ of 0.55).

Low-risk HPV types were nearly two times more common in self-collected than in clinician-collected specimens tested by RLBA (26% versus 14% [$P = 0.004$]) (Table 3); consequently, agreement between clinician-collected and self-collected specimens for detection of low-risk HPV types was worse than for high-risk types (κ , 0.60 versus 0.73 [$P < 0.0001$]). Tampons had higher agreement for low-risk types (91.4%; κ , 0.73) than did swabs (82.2%; κ , 0.49 [$P = 0.07$]; data not shown). For specific high-risk types, self-sampling performed best for HPV-16 and -59 and worst for HPV-31 and -33 (Table 3).

The strongest predictor of self-sampling performance was HPV viral load in the clinician-collected specimens, as estimated by HC2 RLU. HC2 testing of self-collected specimens identified 46% of HC2-positive clinician-collected specimens

TABLE 2. Agreement and comparison of performance of self-collected specimens with that of clinician-collected specimens for detection of high-risk HPV for indicated self-sampling methods^a

Test	Group	Self-collected result	No. of clinician-collected specimens with indicated result		Sensitivity (95% CI)	Specificity (95% CI)	% Concordance	κ (95% CI)	Overall κ (95% CI)
			+	-					
HC2	Tampon (<i>n</i> = 226) ^b	+	47	12	59.5† (47.9–70.4)	91.8* (86.2–95.7)	80.5‡	0.55 (0.43–0.66)	0.58 (0.50–0.66)
		-	32	135					
	Swab (<i>n</i> = 222)	+	67	24	79.8† (69.6–87.8)	82.6* (75.2–88.5)	81.5	0.61 (0.50–0.72)	
		-	17	114					
RLBA ^c	Tampon (<i>n</i> = 93)	+	25	6	86.2 (68.3–96.1)	90.6 (80.7–96.5)	89.2	0.75 (0.61–0.90)	0.73 (0.63–0.83)
		-	4	58					
	Swab (<i>n</i> = 90)	+	32	6	82.1 (66.5–92.5)	88.2 (76.1–95.6)	85.6	0.71 (0.56–0.85)	
		-	7	45					

^a Symbols: *, $P < 0.05$ (Fisher exact test for tampon versus swab); †, $P < 0.01$ (Fisher exact test for tampon versus swab); ‡, $P < 0.001$ (McNemar test for self-collected versus clinician-collected results).

^b Two women from the tampon group had invalid HPV results and are not included in these analyses. One had an invalid result with her clinician-obtained brush, and another had an invalid result with her tampon.

^c RLBA is defined as positive when positive for any high-risk type of HPV.

TABLE 3. Percent concordance between and κ statistics for RLBA results from clinician-obtained and self-obtained specimens for indicated HPV types

HPV type	Total prevalence [no. (%)] (<i>n</i> = 183)		% Concordance	κ (95% CI)
	Clinician (+)	Self (+)		
High-risk types				
Any	68 (37.2)	69 (37.7)	87.3	0.73 (0.63–0.83)
16	9 (4.9)	9 (4.9)	98.9	0.88 (0.72–1.00)
18	12 (6.6)	15 (8.2)	97.3	0.80 (0.63–0.97)
31	7 (3.8)	5 (2.7)	97.8	0.66 (0.34–0.97)
33	4 (2.2)	3 (1.6)	98.3	0.56 (0.12–1.00)
35	10 (5.5)	8 (4.4)	97.8	0.77 (0.55–0.99)
39	7 (3.8)	9 (4.9)	97.8	0.74 (0.49–0.98)
45	14 (7.7)	16 (8.7)	97.8	0.86 (0.72–0.99)
51	7 (3.8)	7 (3.8)	98.9	0.85 (0.65–1.00)
52	11 (6.0)	15 (8.2)	97.8	0.83 (0.68–0.99)
56	7 (3.8)	7 (3.8)	98.9	0.85 (0.65–1.00)
58	14 (7.7)	11 (6.0)	96.2	0.70 (0.49–0.91)
59	6 (3.3)	7 (3.8)	99.4	0.92 (0.77–1.00)
68	7 (3.8)	7 (3.8)	98.9	0.85 (0.65–1.00)
73	5 (2.7)	5 (2.7)	98.9	0.79 (0.52–1.00)
82	3 (1.6)	4 (2.2)	99.5	0.85 (0.57–1.00)
Probable high-risk types				
Any	19 (10.4)	20 (10.9)	96.2	0.80 (0.66–0.94)
26	1 (0.6)	1 (0.6)	100	1.00 (1.00–1.00)
53	11 (6.0)	12 (6.6)	96.2	0.68 (0.45–0.90)
66	8 (4.4)	9 (4.9)	99.4	0.94 (0.82–1.00)
Low-risk types				
Any	26 (14.2)	48 (26.2)	86.9	0.60 (0.47–0.74)
6	5 (2.7)	6 (3.3)	98.3	0.72 (0.42–1.00)
11	1 (0.6)	1 (0.6)	100	1.00 (1.00–1.00)
40	2 (1.1)	4 (2.2)	98.9	0.66 (0.22–1.00)
42	1 (0.6)	4 (2.2)	98.4	0.39 (0.00–0.94)
54	5 (2.7)	7 (3.8)	98.9	0.83 (0.59–1.00)
55	7 (3.8)	13 (7.1)	96.7	0.68 (0.45–0.92)
57	0	0		
83	8 (4.4)	19 (10.4)	94.0	0.56 (0.34–0.79)
84	6 (3.3)	18 (9.8)	92.4	0.39 (0.14–0.63)

with low viral load (RLU, 1 to 9.9) and more than 90% of specimens with high viral load (RLU, ≥ 100). The linear trend was strongly statistically significant ($P < 0.001$).

Table 4 shows the prevalence of HPV types by cytology result for the 183 women with RLBA data. Forty-five percent of 183 women tested positive for HPV by RLBA with clinician-obtained specimens: 37% had at least one high-risk HPV type, 10% had at least one probable high-risk type, and 17% were positive for two or more types. Women with HPV had from one to eight types identified: 42 of the 83 (51%) women with a positive clinician-obtained specimen by RLBA tested positive for one type, 17 (21%) tested positive for two types, 8 (10%) tested positive for three types, 6 (7%) tested positive for four types, 4 (5%) tested positive for five types, and 5 (6%) tested positive for six to eight types. The most prevalent high-risk HPV types in clinician-collected specimens were HPV-58 (7.7%), -45 (7.7%), -18 (6.6%), -52 (6.0%), -35 (5.5%), and -16 (4.9%). The same six types were also the most prevalent in self-collected specimens (Table 4). HPV-16 did not rank among the four most prevalent types overall or when tabulated separately for women over and under 30 years of age.

All 15 women diagnosed with HSIL by cytology tested positive for high-risk HPV using the clinician-obtained specimens with HC2, while 11 out of 15 (73%) tested positive using self-obtained specimens (data not shown). Almost half (seven women) had used a tampon, and half (eight women) had used a swab. Of the four women whose self-obtained specimens did not test positive, three had used tampons and one a swab. Of the six women with HSIL that had RLBA performed, all tested positive for HPV with clinician-obtained specimens, while five out of six (83%) tested positive by self-obtained specimens. Three of the six women with HSIL tested positive for HPV-16 or -18.

DISCUSSION

Self-sampling with swabs produced results similar to those of clinician sampling when combined with either HC2 or RLBA

TABLE 4. Prevalence of HPV types according to RLBA by cytology result and method of specimen collection^a

HPV type	Prevalence [no. (%)]					
	Normal (<i>n</i> = 151)		LSIL/AGUS/ASCUS (<i>n</i> = 24) ^b		HSIL (<i>n</i> = 6)	
	Clinician (+)	Self (+)	Clinician (+)	Self (+)	Clinician (+)	Self (+)
High-risk types						
Any	49 (32.5)	51 (33.8)	12 (50.0)	12 (50.0)	6 (100)	5 (83.3)
16	6 (4.0)	6 (4.0)	2 (8.3)	2 (8.3)	1 (16.7)	1 (16.7)
18	10 (6.6)	12 (8.0)	0	1 (4.2)	2 (33.3)	2 (33.3)
31	5 (3.3)	5 (3.3)	1 (4.2)	0	1 (16.7)	0
33	1 (0.7)	2 (1.3)	1 (4.2)	0	2 (33.3)	1 (16.7)
35	7 (4.6)	5 (3.3)	1 (4.2)	1 (4.2)	2 (33.3)	2 (33.3)
39	5 (3.3)	6 (4.0)	1 (4.2)	3 (12.5)	1 (16.7)	0
45	10 (6.6)	12 (8.0)	2 (8.3)	2 (8.3)	2 (33.3)	2 (33.3)
51	4 (2.7)	4 (2.7)	2 (8.3)	2 (8.3)	1 (16.7)	1 (16.7)
52	8 (5.3)	12 (8.0)	3 (12.5)	3 (12.5)	0	0
56	6 (4.0)	6 (4.0)	1 (4.2)	1 (4.2)	0	0
58	11 (7.3)	8 (5.3)	1 (4.2)	1 (4.2)	2 (33.3)	2 (33.3)
59	3 (2.0)	4 (2.7)	2 (8.3)	2 (8.3)	0	0
68	5 (3.3)	5 (3.3)	1 (4.2)	1 (4.2)	1 (16.7)	1 (16.7)
73	3 (2.0)	4 (2.7)	2 (8.3)	1 (4.2)	0	0
82	1 (0.7)	2 (1.3)	2 (8.3)	2 (8.3)	0	0
Probable high-risk types						
Any	15 (9.9)	16 (10.6)	3 (12.5)	3 (12.5)	1 (16.7)	1 (16.7)
26	1 (0.7)	1 (0.7)	0	0	0	0
53	9 (6.0)	10 (6.6)	2 (8.3)	2 (8.3)	0	0
66	6 (4.0)	7 (4.6)	1 (4.2)	1 (4.2)	1 (16.7)	1 (16.7)
Low-risk types						
Any	22 (14.6)	39 (25.8)	3 (12.5)	6 (25.0)	1 (16.7)	1 (16.7)
6	5 (3.3)	6 (4.0)	0	0	0	0
11	1 (0.7)	1 (0.7)	0	0	0	0
40	0	1 (0.7)	2 (8.3)	2 (8.3)	0	0
42	1 (0.7)	4 (2.7)	0	0	0	0
54	5 (3.3)	7 (4.6)	0	0	0	0
55	6 (4.0)	12 (8.0)	0	0	1 (16.7)	1 (16.7)
57	0	0	0	0	0	0
83	8 (5.3)	16 (10.6)	0	3 (12.5)	0	0
84	5 (3.3)	14 (9.3)	1 (4.2)	2 (8.3)	0	1 (16.7)

^a Excludes two women with unsatisfactory Pap smear results.^b Includes 1 woman with LSIL, 11 women with AGUS, and 12 women with ASCUS.

testing, with sensitivities of 80% and 84% and κ statistics of 0.61 and 0.71, respectively. A recent meta-analysis of swabs and brushes for the detection of HPV found a similarly high, pooled sensitivity of 74% (19).

Tampons combined with HC2 testing did not perform well in our study, with a sensitivity of only 60% and a κ of only 0.55 compared to clinician sampling combined with HC2 testing. Other studies have found sensitivities for tampons ranging from 67 to 94% (19), with one finding that swabs performed better than tampons (10). We asked women to keep the tampon inserted for 10 min; increasing the length of time the tampon was inserted to 1 h may have improved the HPV testing performance (9). Additionally, self-sampling with tampons did perform well with RLBA. The HC2 test is designed to detect 5,000 copies of the virus, whereas the RLBA is based on PCR and could be expected to detect less than 100 copies. These different detection levels impact the results of self-sampling with tampons, as the tampon specimens were more diluted than the swab specimens.

Low-risk HPV types were more common in self-collected than in clinician-collected specimens tested by RLBA (26%

versus 14% [$P = 0.004$]). Other studies have also shown more low-risk HPV types in self-collected specimens (8). As self-sampling obtains cells and secretions from a larger part of the genital tract, this finding is not surprising. Self-sampling may prove to be a more useful tool than clinician-obtained specimens for surveillance of low-risk HPV types.

The prevalence of HPV in our study population of women 18 to 69 years old was high, with 36% positive for high-risk HPV by HC2 and 45% positive for 1 of 27 types by RLBA. Almost half of the women who tested positive for HPV by RLBA tested positive for two or more types, with some positive for as many as eight types. This proportion of multiple infections is higher than has been found in other studies (17) but should be interpreted cautiously given the small number involved.

Self-sampling was as able to identify high-risk HPV in women with HSIL as was clinician sampling, with almost all women with HSIL testing positive for high-risk HPV. However, a few cases were missed. The strongest predictor of self-sampling performance was HPV viral load, as estimated by the HC2 RLU level. Decreasing the lower detection limit of RLU

for HC2 could improve the performance of self-obtained specimens for primary screening, as it improved the sensitivity; however, it decreased the specificity. Further research would be needed to determine an appropriate level combined with specific self-sampling devices prior to implementation.

Self-sampling performed well in our population for the diagnosis of high-risk HPV and may be a useful tool for reducing the barriers to cervical cancer screening. A recent randomized controlled trial tested the efficacy of a "screen and treat" program, also in a peri-urban area near Cape Town (4). One arm of women was tested for high-risk HPV using clinician-obtained specimens and treated instantly, if positive, with cryotherapy. These women had significantly fewer cases of early-stage cervical cancer than did another group of women asked to return in 6 months for further clinical assessment. Clearly, HPV testing has a role to play in strengthening cervical cancer screening programs, and self-sampling combined with HPV testing should be explored in this context.

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